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| 10/674,087 | 09/29/2003 | Jianzhu Chen | 0492611-0507 (MIT 10396) | 2178 |

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| EXAMINER | |
|---|---|
| CHONG, KIMBERLY | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1635 | |

| NOTIFICATION DATE | DELIVERY MODE |
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| 08/07/2009 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@choate.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/674,087 | CHEN ET AL. | |
| | Examiner | Art Unit | |
| | KIMBERLY CHONG | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *38-49,81-90 and 98-102* is/are pending in the application.

4a) Of the above claim(s) *43-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-42,49,81-90,98-102* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Request for Continued Examination*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06/29/2009 has been entered.

### *Status of Application/Amendment/Claims*

Applicant's response filed 06/29/2009 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 12/29/2008 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 38-42, 49, 81-90 and 98-102 are under examination and claims 43-48 and the non-elected subject matter are withdrawn as being drawn to a non-elected invention.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 38-42, 49, 81-90 and 98-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abe et al. (European Journal of Pharm. Sci, 2001 of record IDS filed 09/12/2005), Tuschl et al. (WO 02/44321 of record), Astriab-Fisher et al. teach (Biochemical Pharmacology, 2000. Vol. 60, pp.83-90 of record), Lewis et al. (US 2003/0125281), Deonarain et al. (Expert Opinion Ther. Patents 1998, Vol. 8(1): 53-69 of record) and evidenced by Caplen (Expert Opin. Biol. Ther. 2003, 3(4): 575-586) and Trubetskoy et al. (US 2004/0162235).

The claims are drawn to methods of inhibiting a transcript associated with a influenza virus, or methods of treating an influenza virus nucleoprotein or a clinical condition associated with overexpression or inappropriate expression of an influenza transcript, comprising administering an siRNA in combination with a cationic peptide, wherein said administration may be intravenous or intranasal, or is inhaled, or is delivered by aerosol, or wherein said inhibition is in the lung, or not in the lung, or wherein said combination is delivered with a delivery enhancing agent which may be an antibody or fragment or ligand.

Abe et al. teach targeting an antisense compound to a gene encoding the influenza viral nucleoprotein (NP). Abe et al. teach sequence specific inhibition of

expression in vitro using said antisense compounds delivered using liposomes (see Table 2). Abe et al. teach intravenous delivery of antisense compounds to mouse infected with influenza virus and teach a reduction in the viral target mRNA and a decrease in virus titer in the lungs (see pages 65-68). Abe et al. do not teach using a siRNA targeted to a viral nucleoprotein or teach using a siRNA and a cationic peptide, do not teach administration by inhalation or as an aerosol and further do not teach using an antibody or ligand to specifically target a cell.

Tuschl et al. teach the use of siRNA compounds to inhibit gene expression. Tuschl et al. teach siRNA are the new alternative to antisense compounds and have improved efficacy and safety (see page 3). Tuschl et al. teach a method of using siRNA to infect cells of mammals and teach modulating of the function of a target gene in numerous tissues and cells, such as a viral target gene (see page 8). Tuschl et al. teach the siRNA can be delivered using a carrier system (see page 8) and teach the siRNA can be administered by injection or intranasally. Additionally, Tuschl et al. teach a vector capable of expression of a siRNA (see page 7).

Astriab-Fisher et al. teach inhibition of gene expression using oligonucleotides conjugated to cationic peptides. Astriab-Fisher et al. teach one of the major problems with the use of oligonucleotides is delivery to the cytoplasm and nucleus of the cells and teach it was known in the art to try and overcome this problem by complexing the oligonucleotide with liposomes but one major liability with this approach is that liposomes do not work well in the presence of serum and therefore are not effective in vivo situations (see page 83). Astraib-Fisher et al. teach the use of delivery cationic

peptides such as Tat protein and Antennapeida protein which are capable of intracellular delivery of molecules across cell membranes (see page 83-85).

Lewis et al. teach siRNA molecules and teach compositions comprising siRNA and delivery agents such as polycation agents polylysine or peptides that can be used to delivery siRNA into cells to inhibit the expression of a desired gene (see paragraphs 0029-0079). Lewis et al. further teach the use of cell-targeting signals that can be complexed with the siRNA to enhance the cellular binding to receptors on cells (see paragraph 0082).

Deonarain et al. teach the advantages of using ligand-targeted receptor polyplexes for delivery of nucleic acids to specific cells and tissues. Deonarain et al. teach the use of antibodies that specifically target lung epithelial cells and teach generation of complexes comprising nucleic acids for ligand specific gene delivery (se page 64).

It would have been obvious to one of skill in the art to substitute a siRNA molecule for the antisense molecule in the method of inhibiting an influenza viral gene taught by Abe et al. It would have further been obvious to use the cationic peptide to efficiently deliver the siRNA to the cell of interest and further obvious to incorporate an antibody to the peptide-siRNA complex for targeted delivery to a specific cell type.

It was well known at the time of the instant invention that silencing of gene expression using siRNA was more efficient and sequence specific as compared to antisense or ribozyme technologies. One of ordinary skill in the art would have clearly substituted the antisense compound taught by Abe et al. with a siRNA in a method of

inhibiting an influenza viral gene expression in infected organs of a subject. Applicants argue that it would not have bee obvious to simply switch one molecule type for the other because siRNAs and antisense oligonucleotides have different structural characteristics. This argument is not persuasive because while it is true siRNA and antisense oligonucleotides differ in that the prior is double stranded and the later is single stranded, both molecules have the same function: interfere with the expression from a desired gene. Therefore, because as demonstrated by Tuschl et al., siRNAs were known to be more efficient at silencing gene expression, one of ordinary skill in the art at the time the invention was made would have clearly substituted the antisense molecule for a siRNA to target the influenza viral NP gene.

It was further well known that one of the major problems with the use of oligonucleotides is delivery to the cytoplasm and nucleus of the cells and that siRNA has the same delivery issues as antisense oligonucleotides as evidenced by Caplen (Expert Opin. Biol. Ther. 2003, 3(4): 575-586) who states "[m]any of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system, have been problems the gene therapy field has struggled with for over a decade now" (see page 581, last paragraph). It was also well known in the art that using peptide-nucleic acid complexes could overcome these problems and therefore one of ordinary skill in the would have use a

delivery agent as taught by Astriab-Fisher et al. and Lewis et al. to complex with siRNA in the method of inhibiting the influenza NP viral gene.

Moreover, one would have incorporated an antibody that specifically targets lung cells into the complex comprising a siRNA and a delivery cationic peptide to specifically target lung cells in methods of targeting an influenza viral gene give Deonarain et al. teach the advantages of using ligand-targeted polyplexes for specifically ensuring certain cells types are targeted with a nucleic acid.

Applicant's argue there would have been no reason to believe that delivery methods that are successful for single-stranded oligonucleotides would also be successful for substantially double stranded siRNAs. This argument is not persuasive because both molecules are nucleic acid molecules capable of being complexed with delivery agent similarly. Moreover, there would have been a reasonable expectation of success at using a cationic peptide for delivery of a siRNA into cells, given Astriab-Fisher et al. teach delivery of a nucleic acid using a cationic peptide and as evidenced by Trubetskoy et al., who teach routine methods of using compositions comprising siRNA and cationic agents to delivery said siRNA into cells in vivo (see Example 7). Further one would have expected to be able to conjugate any antibody onto a peptide-siRNA complex given Deonarain et al. teach how to conjugate a lung specific antibody onto nucleic acid molecule and teach efficient cell targeting properties.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

***Response to Applicant's Arguments***

***Re: Double Patenting - maintained***

The rejection of claims 38-42, 49, 81-90 and 98-100 as provisionally rejected under the judicially created doctrine of double patenting over claims 12, 22 and 24-27 of copending Application No. 11/259,434 is maintained for the reasons of record. Applicants have stated they refrain from commenting until such time as the rejection matures into an actual rejection.

Thus claims 12, 22 and 24-27 of co-pending Application No. 11/259,434 anticipates claims 38-42, 49, 81-90 and 98-100 of the instant application.

***Re: Claim Rejections - 35 USC § 112 - withdrawn***

The rejection of claims 38-42 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn.

***Re: Claim Rejections - 35 USC § 103 - withdrawn***

The rejection of claims 38-42, 81-83 and 98, 100 and 101 under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al. (US Patent No. 5,194,428), Tuschl et al. (WO 02/44321), Astriab-Fisher et al. teach (Biochemical Pharmacology, 2000. Vol. 60, pp.83-90) and Deonarain et al. (Expert Opinion Ther. Patents 1998, Vol. 8(1): 53-69) is withdrawn in view of the above new rejection.

## *Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Kimberly Chong/
Primary Examiner
Art Unit 1635